Remarks

Claims 1-20 were present in the application as filed. In response to a restriction dated September 21, 2006, Applicants elected the claims of Group I (claims 1-18). Claims 1-20 were pending with claims 19 and 20 being withdrawn from consideration as being drawn to non-elected inventions. New claim 21 is added above and claims 19 and 20 are cancelled. Claims 1-18 and 21 remain pending in the application.

Claim 1 is amended above to add the step of combining the supernatant that is obtained from precipitation of whole blood with a platelet preparation selected from the group comprising a platelet concentrate, platelet poor plasma or platelet rich plasma. Support for the amendment is found in the specification at page 1, paragraph [0003], and page 16, paragraph [0049] et seq., for example.

Claim Objections

Claim 3 is amended above so that the names of the anticoagulants are spelled out.

Rejections under 35 U.S.C. §102

Claims 1, 3, 4, and 12-16 are rejected under 35 U.S.C. §102(b) as being anticipated by Xiao et al.

Xiao et al. teaches recovery of serotonin from anticoagulated whole blood that has been frozen and thawed and deproteinized using perchloric acid followed by centrifugation and collection of the serotonin-containing supernatant. Xiao et al., however, does not teach or suggest that the supernatant has coagulant activity or that the supernatant is used as a coagulant to be combined with a blood or blood derivative such as a platelet preparation for formation of a wound healing composition.

Xiao et al. does not teach or fairly suggest all the steps of the method as currently claimed. Xiao et al., therefore, cannot anticipate the claims, as amended. Withdrawal of the rejection under 35 U.S.C. §102 in view of Xiao et al. is respectfully requested.

Claims 1, 7, 8, 11, 14, 15 and 17 are also rejected under 35 U.S.C. §102(e) as being anticipated by Coelho et al. According to the Office Action, Coelho et al. teach a method for extracting and then dispensing thrombin consisting of taking whole blood, sequestering prothrombin from the whole blood by addition of ethanol, and filtering to separate the precipitate from the supernatant. Applicants disagree.

Coelho et al., teaches "preparing a fraction enriched in prothrombin by use of Ethanol to substantially enhance the concentration of prothrombin and at the same time remove or denature naturally occurring ingredients within plasma, such as Fibrinogen and Antithrombin III which can bind to, block, interfere with or inhibit prothrombin or its subsequent activation to long-term functional thrombin" (col. 6, lines 27-33). Throughout the specification, Coelho et al. refers to the sequestration of prothrombin and subsequent derivation of autologous thrombin *from plasma*, not whole blood (abstract; col. 6, lines 27-30; col. 6, lines 44-47; col. 7, lines 10-16; col. 7, lines 38-40; col. 9, lines 13-17.) Likewise, the description of Coelho's device for obtaining the thrombin repeatedly refers to plasma and not whole blood (col. 9, lines 7-10, lines 36-38, lines 47-50 etc.) Coelho et al. does not provide any evidence from which one of skill in the art would conclude that precipitation of whole blood was either desirable or advantageous for the preparation of autologous thrombin.

Whole blood and plasma represent distinctly different starting materials. Because Coelho et al. is enabled with respect to use of plasma for the preparation of thrombin, the method of Coelho et al. is not enabled with respect to whole blood. Whole blood is a complex mixture of cells and extra-cellular constituents that remain relatively unaltered upon collection with an anticoagulant. 35-45% of the volume of whole blood is composed of red blood cells; 35% of the red blood cell is hemoglobin. Mechanical or chemical disruption of the red blood cells in whole

blood, for example, by precipitation, results in cell debris and release of hemoglobin into the prep.

Plasma, on the other hand, is the virtually cell-free supernatant of anticoagulated blood obtained after centrifugation to remove red blood cells.

In response to the previous Office Action, Applicants argued that at the time of the invention by Applicants, isolation of plasma from whole blood prior to further processing was standard in the art for preparing fibrin sealant materials from blood. In support of this position, Applicants submitted two documents to establish the state of the art at the time of the invention.

Firstly, a Declaration Under 37 CFR §1.132 was submitted to establish that at the time the present application was filed, one of skill in the art would have recognized that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation from which the cells have been removed (Declaration of Sherwin V. Kevy, M.D. June 13, 2007, paragraph 12) and that prior to 2006, no report of a method using whole blood without the plasma isolation step had been made; the standard of practice in the art for production of thrombin from whole blood included a plasma isolation step for the removal of cells/cell debris prior to precipitation of protein components, leaving soluble thrombin in the supernatant.

Additionally, Applicants submitted in support of the state of the art an article by It wasn't until 2006 that ThermoGenesis (owner of Coelho patent) scientists, Kumar and Chapman, (JECT 39:18-23, 2007, a duplicate copy of which is enclosed for the Examiner's convenience) first reported generating autologous human thrombin from whole blood as the starting material (abstract). The Kumar reference represents the first disclosure of that which Applicants had already invented.

The abstract of the Kumar article states:

"Thrombin-based clotting agents currently used for topical hemostasis with absorbable sponges, fibrin sealants, and platelet gels *are primarily derived from bovine or pooled human plasma sources*...The goal of our research was to develop a rapid, reliable, and simple to perform process to generate autologous human thrombin in the intra-operative setting, *from patient whole blood as the starting source material*." [emphasis added]

"In this study, we have developed a reliable technique to generate autologous human thrombin in the intra-operative setting *from whole blood instead of plasma as the starting source material* within a 30-minute period." [emphasis added]

In Applicants' view, the Kumar and Chapman reference represents the first disclosure other than Applicants', of a method for extracting thrombin from whole blood.

Applicants urge, therefore, that the Declaration of Dr. Kevy, and Kumar reference, already of record in this case, when taken together establish that, at the time of the disclosure by Coelho et al. of a method for extracting thrombin from blood, the skilled artisan would not have thought it feasible let alone advantageous precipitate plasma proteins without first removing blood cells, i.e. isolating the plasma fraction.

Coelho et al. does not teach a method for the extraction of thrombin by precipitation of whole blood and therefore, cannot anticipate Applicants' claimed method.

Rejection under 35 U.S.C. §103

Claims 1, 2, and 7-18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gray *et al.* (US 4,680,177) in view of Cochrum *et al.* (US 5, 773,033). Specifically, the Office Action asserts that it would have been obvious to one of skill in the art to combine the anticoagulant strategy taught by Gray *et al.* with the method of isolating fibrinogen from blood by ammonium sulfate precipitation as taught by Cochum *et al.*

Gray *et al.* teaches the use of neutral salts that do not bind calcium as anticoagulants in the collection of whole blood. Gray *et al.* teaches that the anticoagulated blood is centrifuged in the conventional way to separate the cells from the plasma (Step 2, col. 11, lines 30-34.) Similarly, Cochum *et al.* teaches that autologous fibrinogen is prepared from the patient's own blood which is separated into plasma, platelets and blood cells. The plasma is further processed to yield purified fibrinogen isolated from other plasma proteins. (col. 7, lines 53-56; col. 10, lines 6-10.)

Thus, Gray et al. does not teach precipitation of whole blood without a plasma isolation step.

Claims 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock as applied to claims 1-4 and 7-18 and further in view of Sato et al. The disclosure of Coelho et al. is discussed above.

Rock et al., describes a method for the stabilization of Factor VIII activity in whole blood or blood plasma. Following the observation that the stability of Factor VIII was adversely effected by collection of blood with anticoagulants that chelated calcium from the blood, Rock et al. developed a method for blood collection that includes mixing the blood (following collection of the blood with a chelating anticoagulant, for example, citrate anticoagulants and EDTA) with a calcium-heparin solution, whereby calcium is restored to physiologic levels in the presence of a non-chelating anticoagulant (heparin). Rock et al. does not relate to the precipitation of either whole blood or plasma for the recovery of a coagulant material like thrombin.

Sato et al. describes the benefit of reduced hemolysis by adding glycerin and mannitol to a blood preservation solution.

To the extent both Rock et al. and Sato et al. relate to anticoagulant preparations commonly used in the art, but not to mixing of whole blood with a precipitating agent to obtain a supernatant containing a coagulant, they do not compensate for the shortcomings in the teachings of Coelho et al.

None of the references cited herein teach or fairly suggest that a coagulant, for example, thrombin can be extracted from whole blood by precipitation of the whole blood without the intermediate plasma isolation step.

Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Double Patenting

Claims 1, 3 and 4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-18 and 20 of copending application no. 11/200,535. The provisional rejection is duly noted with appropriate action to be taken upon allowance of the present claims.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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